Remarks

The Office Action mailed January 7, 2009 has been received and reviewed. Claims 34-44, 67-69, 71-82, and 84-102 are pending and under consideration. Reconsideration and withdrawal of the rejections are respectfully requested.

Interview Summary

Applicants thank Examiner Leith for the courtesy of a telephonic interview held April 17, 2009. Inventors Daryll Emery, Ph.D. and Darren Straub, Ph.D., and Applicants' undersigned representative Christopher Gram participated on behalf of Applicants.

All of the pending claims and outstanding rejections were discussed, although the rejections based, at least in part, on Genovese *et al.* were discussed in particular. No agreement on claims was reached, but Examiner Leith agreed that Genovese *et al.* fails to provide teaching related to adaptive immunity.

The substance of Applicants' remarks during the interview are reflected in the remarks that follow.

The 35 U.S.C. §103 Rejection

Claims 34, 37, 39-43, 67-69, 83-86, 89, 91-95, and 97-102 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Emery *et al.* (U.S. Patent No. 5,830,479) in view of Phelps *et al.* (U.S. Patent No. 5,339,766) in view of Genovese *et al.* (1998) in light of Sharma *et al.* (U.S. Patent No. 4,458,630). Applicants respectfully traverse.

Claims 34-44, 67-69, 71-82, and 84-102 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Emery *et al.* (U.S. Patent No. 5,830,479) in view of Phelps *et al.* (U.S. Patent No. 5,339,766) and further in view of Evans *et al.* (U.S. Patent No. 6,500,438) in view of Genovese *et al.* (1998) in light of Sharma *et al.* (U.S. Patent No. 4,458,630). Applicants respectfully traverse.

Claims 34, 69, and 84 are independent. Each of the remaining claims depends, directly or indirectly, from one of the independent claims and, therefore, includes all of the features recited in the independent claim and any intervening claim from which it depends. Thus, remarks that refer to one or more of the independent claims apply equally to any claim that depends from an identified independent claim.

Applicants respectfully submit that the suggested combination of references fails to establish a *prima facie* case of obviousness for at least the reasons of record, which were more thoroughly discussed during the interview and are reiterated in the remarks that follow.

The Office Action asserts that Applicants' remarks regarding these rejections in the response filed October 10, 2008 were unpersuasive. In partial reply, the Office Action reiterates the assertion that Emery *et al.* would motivate one skilled in the art to innoculate successive generations *in ovo* using siderophore receptor antigens. The Office Action further asserts, "Inoculation of an egg with a siderophore receptor present in a chicken previously inoculated when it was an embryo with the same siderophore receptor would necessarily contain maternal antibodies to the siderophore receptor." (Office Action, page 6). Applicants interpret this statement to mean that the Office Action asserts that a hen inoculated *in ovo* against a siderophore receptor will necessarily pass maternal antibodies against the siderophore receptor to her own eggs. If Applicants' interpretation misconstrues the Office Action's position, Applicants' respectfully request clarification and that a subsequent Office Action be issued as non-final in order to give Applicants a fair opportunity to respond to the clarified position. The Office Action provides no technical support for the position that a hen inoculated *in ovo* against a particular antigen will pass maternal antibodies against that particular antigen to her eggs. Applicants respectfully submit that this premise is incorrect.

The fact that a hen has been immunized–whether *in ovo* or at any time during her life–against a particular antigen does not provide any information about the presence and/or content of maternal antibodies that she may pass to an egg. Humoral antibodies raised against an antigen do not persist in the individual indefinitely. Adaptive immune memory is provided by

the circulation of B cells that can recognize the antigen upon subsequent exposure to the antigen and thereafter generate a new and transient burst of humoral antibody against the antigen. The half-life of typical circulating humoral antibodies is on the order of days (e.g., 10 to 30 days). Thus, circulating humoral antibodies produced as a result of *in ovo* inoculation are catabolized long before an *in ovo*-inoculated chick can mature and lay eggs, even though the *in ovo*-inoculated bird remains protected against subsequent exposure to the antigen by circulating B cells. Consequently, while it may have been within the skill of the ordinary artisan to inoculate successive generations of eggs *in ovo* against siderophore receptor antigens, doing so does not teach or suggest that each successive generation of eggs will possess maternal antibodies against the siderophore receptor antigens.

The Office Action states that "the crux of the Genovese *et al.* publication is to vaccinate young poults against bacterial infection; namely, *Salmonella enteriditis*." (Office Action, page 7). This is incorrect.

Genovese *et al.* acknowledge the difficulty of vaccinating young poults because "the typical humoral/cell-mediated [i.e., adaptive] immune response requires 7 to 10 days to reach protective levels while poultry have been shown to be most susceptible to bacterial species such as Salmonella during the first 4 days of life. In addition, maternal antibodies may cause interference with the vaccine and the desired immune response to that vaccine." (Genovese *et al.*, page 5). Thus, Genovese *et al.* acknowledge exactly the technical problem that Applicants' methods are designed to overcome. Genovese *et al.*, however, adopt an approach to overcoming the problem that is different than Applicants' approach. Rather than attempting to influence the adaptive immune response, as Applicants do, Genovese *et al.* attempt to influence the non-specific innate immune response to compensate for the lack of effective adaptive immune response. Genovese *et al.* thus prime aspects of the non-specific innate immune response by administering immune lymphokines (ILKs). ILKs have no effect on the adaptive immune response that is the subject of Applicants' claims.

The Office Action directs Applicants' attention to page 3 of Genovese *et al.*, where it is asserted that "day old turkey poults were challenged with SE (Salmonella enteriditis). Vaccination with a foreign antigen will necessarily produce an innate as well as adaptive immune response." (Office Action, page 3). The Office Action further states, "[A] vaccination has already been given to the poults in the time required by the claimed invention. Thus, although Genovese et al. stimulate the immune systems of the bird post-vaccination, the vaccinations have none-the-less been administered[.]" This is incorrect.

First, Genovese *et al.* never vaccinate the poults. The SE challenge is not a vaccination; it is a challenge. Genovese *et al.* perform the challenge thirty minutes after priming the innate immune response in order to assess the extent to which the primed innate immune response protects the poults from challenge with the pathogen because Genovese *et al.* acknowledge that an adaptive immune response at this time is ineffective to protect the poult from infection.

Second, as is discussed in greater detail below, exposure to a foreign antigen does not "necessarily produce an innate as well as adaptive immune response" in embryos or newly hatched chicks. Exposure to a foreign antigen can result instead in immunological tolerance–the absence of an immune response.

For at least these reasons, Applicants respectfully submit that any rejection that depends, even only in part, on Genovese *et al.* fails to establish a *prima facie* of obviousness. Therefore, Applicants respectfully request that the rejection of claims 34, 37, 39-43, 67-69, 83-86, 89, 91-95, and 97-102 under 35 U.S.C. §103(a) as being unpatentable over Emery *et al.* (U.S. Patent No. 5,830,479) in view of Phelps *et al.* (U.S. Patent No. 5,339,766) in view of Genovese *et al.* (1998) in light of Sharma *et al.* (U.S. Patent No. 4,458,630) and the rejection of claims 34-44, 67-69, 71-82, and 84-102 under 35 U.S.C. §103(a) as being unpatentable over Emery *et al.* (U.S. Patent No. 5,830,479) in view of Phelps *et al.* (U.S. Patent No. 5,339,766) and further in view of Evans *et al.* (U.S. Patent No. 6,500,438) in view of Genovese *et al.* (1998) in light of Sharma *et al.* (U.S. Patent No. 4,458,630) be reconsidered and withdrawn.

Claims 34, 37, 39-43, 67-69, 83-86, 91-95, and 97-102 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Emery *et al.* (U.S. Patent No. 5,538,733) in view of Emery *et al.* (U.S. Patent No. 5,830,479) in view of Phelps *et al.* (U.S. Patent No. 5,339,766). Applicants respectfully traverse.

Claims 34-44, 67-69, 71-82, and 84-102 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Emery *et al.* (U.S. Patent No. 5,830,479) in view of Phelps *et al.* (U.S. Patent No. 5,339,766) in view of Emery *et al.* (U.S. Patent No. 5,538,733) and further in view of Evans *et al.* (U.S. Patent No. 6,500,438). Applicants respectfully traverse.

Claims 34, 69, and 84 are independent. Each of the remaining claims depends, directly or indirectly, from one of the independent claims and, therefore, includes all of the features recited in the independent claim and any intervening claim from which it depends. Thus, remarks that refer to one or more of the independent claims apply equally to any claim that depends from an identified independent claim.

Applicants respectfully submit that neither the combination of the '733 patent, the '479 patent, and the '766 patent nor the combination of the '479 patent, '766 patent, '733 patent, and '438 patent provide one skilled in the art with a reasonable expectation of success performing the methods recited in claims 34, 69, and 84.

The Office Action asserts that the '733 patent discusses the problem of vaccinating young animals because of the influence of maternal antibodies and proposes a solution involving administering vaccines present in a sustained and/or delayed delivery vehicle to young poultry at 1-90 days of age. (Office Action, page 13). The Office Action further asserts that the '733 patent teaches that the immunized poultry possess maternal antibody to the antigen and that SRPs are suitable immunogens for implantation. (Office Action, page 14). The Office Action acknowledges that the '733 patent fails to teach that the implant can be administered *in ovo*, the specific injection times recited in claims 39-42 and 44, the administration of a second dose of immunogen, or the inclusion of porins in the vaccine. (Office Action, page 15).

The Office Action further asserts that the '479 patent teaches a method of immunizing poultry using SRPs, and further teaches that SRPs can be administered using sustained release and, separately, that the SRPs can be delivered *in ovo*. (Office Action, page 16). Also, the '766 patent (Phelps *et al.*) is asserted to teach methods for introducing material into poultry eggs. (Office Action, page 17).

The Office Action asserts it would have been obvious to one skilled in the art to modify the method of sustained delivery of SRPs taught in the '733 patent by administering the SRPs *in ovo* according to the '479 patent. (Office Action, page 18). Applicants respectfully disagree.

Applicants disagree that one skilled in the art would have had a reasonable expectation that implanting a device for sustained release of a selected immunogen *in ovo* would successfully induce an effective adaptive immune response against the selected immunogen, as asserted in the Office Action. For the purposes of the current discussion, Applicants position need not rely on the technical feasibility of *in ovo* delivery methods as taught in the '766 patent, but rather rests on the knowledge of one skilled in the art that immunological tolerance can be induced by vaccinating animals with immature immune systems, particularly embryos. Nevertheless, Applicants reserve the right to argue that the teaching of Phelps *et al.* fails to permit one skilled in the art to successfully deliver a device for sustained release of a selected immunogen *in ovo*.

Immune tolerance to a foreign antigen can occur when a subject is exposed to a foreign antigen under conditions that elicit specific unresponsiveness to the foreign antigen rather than an adaptive humoral immune response to the antigen. In other words, under some circumstances, exposure to a foreign antigen does not necessarily result in the challenged subject mounting an adaptive immune response, but instead results in the subject's immune system perceiving the foreign antigen as "self" and establishing antigen-specific immune non-response.

Many of the conditions under which immune tolerance may be induced are present in the circumstance of *in ovo* vaccination as recited in Applicants' claims. (See, *Microbiology*, fourth edition, Davis *et al.* eds., 1990, J.B. Lippincott Co., Philadelphia, Pennsylvania, pp. 381-382.).

For example, SRPs–the immunogens specifically identified in the Office Action–are monomeric antigens, not aggregated; sustained release implants are not equivalent to injection into tissue, but are more similar to intravenous administration; and *in ovo* administration necessarily results in vaccination of the embryo rather than adult. So, one skilled in the art would recognize that vaccinating embryos or newly-hatched chicks using sustained release implants harbor the risk of inducing immune tolerance to the immunogen in the vaccine rather than raising adaptive immunity against the immunogen. Many of these conditions are present whether the sustained release implant is administered at one day of age (as in the '733 patent) or *in ovo*, as in the present claims.

The difference between vaccinating an egg by sustained release of a selected immunogen from a biocompatible implant at one day of age versus injecting the biocompatible implant *in ovo*–and a compelling reason why one skilled in the art would not extend the teaching of the '733 patent to *in ovo* delivery–is that the risk of inducing immune tolerance to the immunogen is greater when the biocompatible implant containing the immunogen is delivered *in ovo* compared to delivering the biocompatible implant after hatch. One reason for the increased risk of inducing immune tolerance when the biocompatible implant is injected *in ovo* is the different amounts of–and the corresponding effects of the different amounts of–circulating maternal antibody in the embryo versus in the newly-hatched chick.

Each of claims 34, 69, and 84 recites that the egg (or eggs) into which the biocompatible implant is injected comprises maternal antibody to the selected immunogen. Prior to hatch, some of the maternal antibody circulates in the embryo but most remains sequestered in the yolk. At hatching, however, the yolk is fully absorbed and the maternal antibody from the yolk is fully absorbed into the circulation of the chick. Thus, the chick–but not the embryo–has the full passive immunization benefit of the maternal antibodies. Consequently, the circulating maternal antibody environment is very different in the embryo than in the newly-hatched chick and this difference influences the risk of inducing immune tolerance.

As just explained, a day-old chick possesses the full amount of maternal antibody in circulation, including any maternal antibody specific to the selected immunogen. When a day-old chick is vaccinated with a biocompatible implant providing sustained release of the selected immunogen, maternal antibodies against the selected immunogen, if present, clear the immunogen from the chick's circulation without involving the chick's immature immune system, thereby reducing the risk of inducing immune tolerance to the selected immunogen. In contrast, when a biocompatible implant is provided *in ovo*, the level of maternal antibody absorbed by the chick–e.g., at day 20 of incubation as described in Example 4–is incomplete and, as a consequence, the embryo is at risk for developing immune tolerance to the immunogen in the biocompatible implant rather than adaptive immunity against the immunogen.

At least two factors put the embryo at greater risk for inducing immune tolerance to the selected immunogen than a newly-hatched chick receiving the very same sustained release implant. First, the embryo's immune system is less mature and, therefore, is less capable of raising an adaptive response to a foreign antigen and is more susceptible to inducing immune tolerance to the foreign antigen. Second, the immune system of an embryo is less protected from the foreign antigen by maternal antibodies, if present at all, than the immune system of a day old chick. Each factor, alone, is sufficient to render the effect of administering the sustained release implant to an embryo unpredictable. Taken together, however, one skilled in the art could not have predicted that vaccinating eggs using the recited implant would provide effective vaccination rather than inducing immune tolerance.

Thus, prior to Applicants' disclosure, it was unpredictable whether injecting a biocompatible implant containing a selected immunogen into an egg that possesses maternal antibody against the selected immunogen could induce an adaptive immune response against a selected immunogen or, alternatively, whether doing so would induce immune tolerance to the selected immunogen.

Because the combination of the '733 patent and the '479 patent fail to provide one skilled in the art with a reasonable expectation that injecting a biocompatible implant containing a

selected immunogen *in ovo* would induce an effective adaptive immune response rather than inducing immune tolerance, the combination does not help establish a *prima facie* case of obviousness against claims 34, 69, and 84. Nothing in Phelps *et al.* or Evans *et al.* cures this deficiency in the combined teachings of the '733 patent and the '479 patent.

As explained by Dr. Emery during the interview, the methods recited in claims 34, 69, and 84 permit those in the poultry industry to vaccinate a generation of eggs, at one time, and ensure that the resulting chicks can raise an adaptive immune response against a selected immunogen at the time–which can vary from egg to egg in a single generation from a single hen–when maternal antibody to the selected immunogen wanes. In the absence of such sustained release vaccination methods, those in the industry must otherwise vaccinated each chick every day over a multi-week period to ensure protection for the entire new generation because the waning of maternal antibody, if ever present at all, can vary from chick to chick.

Applicants respectfully submit that claims 34, 37, 39-43, 67-69, 83-86, 89, 91-95, and 97-102 are patentable under 35 U.S.C. §103(a) over Emery *et al.* (U.S. Patent No. 5,830,479) in view of Phelps *et al.* (U.S. Patent No. 5,339,766) in view of Genovese *et al.* (1998) in light of Sharma *et al.* (U.S. Patent No. 4,458,630); claims 34-44, 67-69, 71-82, and 84-102 are patentable under 35 U.S.C. §103(a) over Emery *et al.* (U.S. Patent No. 5,830,479) in view of Phelps *et al.* (U.S. Patent No. 5,339,766) and further in view of Evans *et al.* (U.S. Patent No. 6,500,438) in view of Genovese *et al.* (1998) in light of Sharma *et al.* (U.S. Patent No. 4,458,630); claims 34, 37, 39-43, 67-69, 83-86, 91-95, and 97-102 are patentable under 35 U.S.C. §103(a) over Emery *et al.* (U.S. Patent No. 5,538,733) in view of Emery *et al.* (U.S. Patent No. 5,830,479) in view of Phelps *et al.* (U.S. Patent No. 5,339,766); and claims 34-44, 67-69, 71-82, and 84-102 are patentable under 35 U.S.C. §103(a) over Emery *et al.* (U.S. Patent No. 5,830,479) in view of Phelps *et al.* (U.S. Patent No. 5,339,766) in view of Emery *et al.* (U.S. Patent No. 5,538,733) and further in view of Evans *et al.* (U.S. Patent No. 6,500,438). Accordingly, Applicants respectfully request that each of the pending rejections be reconsidered and withdrawn.

Summary

Applicants respectfully submit that the pending claims 34-44, 67-69, 71-82, and 84-102 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives at the telephone number listed below if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted
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